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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,644	02/28/2005	Kunihiro Ohta	04393/0202300-US0	7488

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EXAMINER	
LEAVITT, MARIA GOMEZ	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,644	OHTA ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-16* is/are pending in the application.

4a) Of the above claim(s) *1 and 3-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2 and 13-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05-05-08;05-28-08;05-05-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Applicants' amendment filed on 05-05-2008 has been entered.
3. Status of claims. Claims 1-11 and 13-16 are currently pending. Claims 2, 13, 15, and 16 have been amended; claim 12 has been canceled and claims 1 and 3-11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention by applicants amendment filed on 05-05-2008.
4. The examiner appreciates Applicants' phone call to clarify the status of claim 1 that was inadvertently cited as rejected instead of claim 2, under rejection of claims 1 and 15 under 35 U.S.C. 103(a).
5. Therefore, claims 2 and 13-16 are currently being examined to which the following grounds of rejection are applicable.

Withdrawn rejections in response to Applicant arguments or amendments.

Specification Objection

In view of Applicants' amendment of the specification at page 11, lines 5-7, (paragraph [0056] on page 5 of the U.S. Patent Application Publication No. 2006/0183225) and at page 5, line 21 (paragraph [0026] on page 2 of the '225 Publication), to spell out the abbreviation "TSA", objection to the specification has been withdrawn.

Claim Rejections - 35 USC § 112- Second Paragraph

In view of Applicants' amendment of claim 16, rejection of claim 16 under 35 U.S.C. 112, second paragraph, has been withdrawn.

Claim Rejections - 35 USC § 112, Enablement

In view of Applicants' amendment of claims 2 and 16 to introduce the limitations "chicken-derived B cells" and "a histone deacetylase inhibitor", rejection of claims 2 and 13-16 under 35 U.S.C. 112, first paragraph, scope of enablement, has been withdrawn.

In view of the withdrawn rejection, applicants' arguments are rendered moot.

Objection/Rejections maintained in response to Applicant arguments or amendments.

Information Disclosure Statement

The information disclosure statements filed on 05-28-2008 and 05-05-2008 have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copies. The reference cited as CA in the disclosure filed on 05-05-2008, has been considered to the extent that an English abstract has been provided.

Claim Rejections - 35 USC § 103

Claims 2 and 15 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304).

Response to Applicants' arguments as they relate to rejection of claims 2 and 15 under 35 USC § 103

At page 11 of Remarks, Applicants contend that the combination of Sonoda et al., McMurry et al., and Watson et al. do not obviate the instant invention because "a skilled artisan would not have been able to predict the precise manner in which the elements that the Examiner points to in the cited prior art should have been combined to arrive at the claimed methods because V(D)J recombination and homologous recombination are different mechanisms. Specifically, the skilled artisan would not have looked to the teachings of Watson or McMurry, to which the Examiner points, for guidance to arrive at the claimed methods because V(D)J recombination (in both B cells and T cells) and homologous recombination are different mechanisms". Moreover, in relation to the differences between V(D)J recombination (in both B cells and T cells) and homologous recombination, Applicants allege that "V(D)J recombination requires functions of a "site-specific endonuclease", called RAG1-RAG2, which triggers DNA break formation by a mechanism similar to the mechanism of transposition, in addition to other factors such as Ku and Artemis. On the other hand, the mechanism of gene conversion requires activation induced cytidine deaminase (AID) and other factors involved in homologous recombination (e.g., XRCC3)" . In addition Applicants refer for support of their position to the following publications: Gellert (2004, lmmunoL Rev., 200:233-248) and Bassing et al. (2002, Cell, v.109 Supph 44-55)[emphasis added] . Such is not persuasive.

Applicants' position is that the molecular mechanisms for V(D)J recombination are entirely different from gene conversion in part because "site-specific endonuclease", called RAG1-RAG2 are required for V(D)J recombination whereas gene conversion requires activation

induced cytidine deaminase (AID). Though the examiner agrees with Applicants that RAG is functional only in VDJ recombination at the Ig locus in mice and humans by a single homologous recombinant event due to rearrangement of antibody light chain genes, i.e., a single V to a single J, or rearrangement of the heavy chain genes i.e., a single D to a single J and then a single V to the fused D-J segment, generating a functional VJ or VDJ product, which is different to the mechanism of AID, active in gene conversion in chickens (e.g., possessing only one functional V region), where diversification of the V region is accomplished by successive homologous recombination with upstream pseudo genes, and AID is also active in somatic hypermutation and class-switch (Martin et al., 2002, Nature Review, pp.605-614; page 605, col. 1; p. 606, Fig. 1; page 608, col. 1 and 2, Table 1; p. 612, col. 2, last paragraph), both recombinant enzymes require accessibility to the double stranded DNA to induce DNA breaks. Therefore, relaxing the chromosomal DNA using deacetylase inhibitors should be reasonably expected to improve AID mediated recombination for the same reason it improves RAG mediated VDJ recombination by facilitating access of both recombinant enzymes to the chromosomal DNA.

At page 12 of Remarks, Applicants argue regarding V(D)J recombination that " it was thought that histone acetylation would not be sufficient for relaxation of chromatin. Thus, Bassing et al. (2002) teaches away from the use of histone acetylation to enhance gene conversion. See also, McMurry and Senoo et al. 2001, Int. Immunology, 12(11): 1405-1414 (copy filed herewith in IDS referred to in the foregoing comments), both of which are cited by Bassing et al (2002). Thus, one of ordinary skill in the art would not have been motivated to use histone acetylation to enhance gene conversion. Taken together, a skilled worker at that time of

filing of the priority document of the current application would not have looked to Watson or McMurry for guidance about enhancing homologous recombination because these references teach only enhancement of a different and unrelated mechanism, V(D)J recombination. Thus, a skilled artisan would not have had an expectation of success based upon the teachings of Watson or McMurry that gene conversion (i. e., homologous recombination) in chicken-derived B cell lines e.g., DT-40 cells) could have been enhanced by hyperacetylation of histones using a histone deacetylase inhibitor (e.g., trichostatin (TSA)) "[emphasis added]. Such is not persuasive.

Applicants have referred to the Bassing et al. (2002) publication, disclosing the mechanism of chromosomal V(D)J recombination. However, applicants do not set forth where in the document the author teaches away from the instant invention by stating that "histone acetylation would not be sufficient for relaxation of chromatin". In contrast to applicant arguments, McMurry discloses that V(D)J recombination is initiated by the recombinase RAG. Moreover, McMurry teaches that hyperacetylation of histones enhances chromosomal accessibility to the recombinase. Hence, if hyperacetylation enhances V(D)J recombination by RAG in the T cell receptor, immunoglobulin coding segments (V, D, and J) and flanking recombination signals (p.495, col. 1, first paragraph) by making chromosomal DNA more accessible, then hyperacetylation induced by histone deacetylase should be reasonably expected to improve AID mediated recombination for the same reason it improves RAG mediated VDJ recombination. Thus, is unclear how hyperacetylation will prevent the claimed procedure from being successful.

At pages 12 and 13 of Remarks, Applicants contend that "Additionally, it is respectfully pointed out that the state of the art at the time of filing of Japanese patent application no. JP

2002-221232, which is the priority application of the current application undergoing prosecution, provided no guidance or expectation of success for designing or using the claimed methods to prepare diverse antibodies including antigen-specific antibodies from DT40 cells. The differences between the prior art and the pending claims are significant because the prior art provides no guidance or expectation of success for making or using the methods as called for by the present claims; and the level of ordinary skill in this art is relatively high. See KSR Int'l Co. v. Teleflex Inc., 127 s. Ct. 1727, 1734 (2007); Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 15-17 (1966). The guidance that is missing in the cited prior art documents is found in the teachings of the present invention (See Embodiments 1-4 of the '225 publication) as well as the teachings of Seo H., et al. 2005, Biotechnology, vol. 23:731-735 (copy filed herewith with IDS referred to in the foregoing comments), a publication, by the named inventors of the current application, that was published after the filing date of the current application and describes the surprising results of the current invention. For the reasons set forth above, even with Sonoda, McMurry, and Watson in hand one of ordinary skill would have been unable to predict that the method of antibody production called for in the present claims would obtain a diverse population of antibodies. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection". Such is not persuasive.

It is Applicants' position that the guidance is missing in the cited prior art documents in relation to the instant invention, in part, because the molecular mechanisms for V(D)J recombination are entirely different from gene conversion and histone acetylation would not be sufficient for relaxation of chromatin. The examiner refers applicants to the reasons of record and the reasons set forth in the paragraphs above for these considerations. Furthermore,

Applicants' position is not persuasive because Applicants' opinion is unsupported by any specific or real evidence, while the options of the skill in the art are given respectful consideration, in the absence of any actual evidence of "unexpected results", the opinions of the inventor do not overcome a case of *prima facie* obviousness. The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997). See **MPEP § 716.01(c)** for examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration. Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant. MPEP 716.01(c).

Claims 13-14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304) as applied to claims 2 and 15 above and further in view of Choy et al., (Mol Cell Biol. 2002, pp 8215-8225) .

Response to Applicants' arguments as they relate to rejection of claims 13 and 14 under 35 USC § 103

At page 11 of Remarks, Applicants contend that "the Examiner attempts to cure the deficiencies of the cited prior art discussed above with Choy. However, nothing in Choy, alone or in combination with the other cited prior art references, describes or suggests the claimed methods for antibody production. Choy teaches transcription of a gene. One of ordinary skill in the art, when looking for a method of enhancing homologous recombination during antibody production, would not seek guidance from a reference relating to a non-analogous art, i.e., gene transcription. Thus, a skilled worker would look to Choy for such guidance. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection". Such is not persuasive.

Choy et al., complements the teachings of Sonoda, McMurry and Watson by disclosing that transcription requires acetylation of histone N-terminal tails to promote an open chromatin conformation. Clearly, a histone deacetylase inhibitor such as trichostatin A will promote relaxation or opening of the chromatin to facilitate access of recombinant enzymes to genes located in said chromatin (e.g., V gene) .

Claim 16 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Sonoda et al., (2001, *Phi. Trans. R. Soc.* London, 2001, 11-117) in view of McMurry et al., (2000, Science 495-498) and further in view of Watson et al., (2001, Recombinant DNA, pp. 297-304) as applied to claims 2 and 15 above and further in view of Sale et al., US Patent 7,122,339, Date of Patent October 17, 2006.

Response to Applicants' arguments as they relate to rejection of claim 16 under 35 USC § 103

At page 14 of remarks, Applicants allege that "the examiner attempts to cure the deficiencies of the cited prior art discussed above with sale. However, nothing in Sale, alone or in combination with the other cited prior art references, describes or suggests the claimed methods. Accordingly, it is respectfully requested that the Examiner reconsider and withdraw this rejection". Moreover, the Examiner is respectfully reminded of the case law, namely, it is only through experiments carried out by the present inventors as described in the specification that the parameters for the inventive methods were determined and tested. MPEP § 2145(X)(B); In re Dow Chemical Co., 837 F.2d 469 (Fed. Cir. 1988). In addition the Examiner is also reminded that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings KSR v. Teleflex, 127 S. Ct 1727 (2007)2 ; (disscussing United States v. Adams, 383 U.S. 39, 40 (1966) (the companion case to Graham), Anderson's Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57 (1969), and Sakraida v. AG Pro, Inc., 425 U.S. 273 (1976)). Furthermore, Applicants conclude that "a skilled worker would not have looked to guidance in arriving at the claimed methods because the mechanisms of V(D)J recombination and homologous recombination are different. As such, a skilled worker would not have had an expectation of success or predictable results if he or she combined the cited prior art" [emphasis added]. Such is not persuasive.

The Examiner refers Applicants to arguments as set forth in the paragraph above and to the reasons of record, as disclosed in the previous office action.

Conclusion

Claims 2 and 13-16 are erejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the

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